METABOLIC SURGERY

Bariatric Surgery in Obese Patients With Type 1 Diabetes

Diabetes Care 2016;39:941–948 | DOI: 10.2337/dc15-2732

John P. Kirwan,[1] Ali Aminian,[2]
Sangeeta R. Kashyap,[1]
Bartolome Burguera,[1,2]
Stacy A. Brethauer,[2] and Philip R. Schauer[2]

OBJECTIVE

There is a paucity of data on the impact of bariatric surgery in type 1 diabetes (T1D). The aim of this review was to quantify the overall effects of bariatric surgery in obese patients with T1D.

METHODS

We searched PubMed, Scopus, ISI Web of Knowledge, and Google Scholar from their inception to December 2015 to identify all relevant studies of bariatric surgery in adult obese patients with T1D.

RESULTS

The review included 17 studies with 107 individuals, including 10 case series and 7 case reports. Overall, the dominant procedure was gastric bypass (n = 70; 65%). All studies reported a significant reduction in excess weight. A significant reduction in weight-adjusted daily insulin requirements was shown in all case series except one. Pooled mean ± SD of pre- and postoperative glycated hemoglobin (HbA_{1c}) for the entire cohort with available data (n = 96) was 8.4 ± 1.3% and 7.9 ± 1.1%, respectively (P = 0.01). In addition to common postoperative complications, profound glycemic changes (diabetic ketoacidosis and hypoglycemia) and gastrointestinal dysmotility symptoms (prolonged ileus and acute gastric remnant dilation) have been reported. No surgical mortality was reported.

CONCLUSIONS

Bariatric surgery leads to significant weight loss in severely obese patients with T1D and results in a significant improvement in insulin requirements and glycemic status. The favorable metabolic effects of bariatric surgery may facilitate medical management of and cardiovascular risk reduction in T1D in the setting of severe obesity. Diabetic ketoacidosis and hypoglycemia are potentially serious complications. Short-term results of bariatric surgery in patients with T1D are encouraging, but larger and longer-term studies are needed.

Patients with type 1 diabetes (T1D) constitute about 5–10% of all cases of diabetes. Large epidemiologic studies indicate that the worldwide incidence of T1D has been increasing in recent decades (1,2). T1D is associated with serious long-term complications that affect the cardiovascular system, eyes, kidneys, and nervous system and predispose to certain infections (3), which can lead to substantial increased mortality rates compared with the nondiabetic population (4,5).

The prevalence of obesity among youth with T1D in the U.S. was found to be 12.6% (6). Overall, approximately 50% of patients with T1D are currently obese or overweight, and between 20 and 40% meet the criteria of metabolic syndrome, depending on the study population and the diagnostic criteria used (7). Excessive

[1]Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH
[2]Bariatric and Metabolic Institute, Cleveland Clinic, Cleveland, OH

Corresponding author: Ali Aminian, aminiaa@ccf.org.

Received 17 December 2015 and accepted 23 January 2016.

J.P.K. and A.A. are co-first authors.

See accompanying articles, pp. 857, 861, 878, 884, 893, 902, 912, 924, 934, 949, and 954.

body weight, which is increasingly seen in patients with T1D, can have an important impact on the course of diabetes (8). Obesity and insulin resistance may accelerate development of T1D in young predisposed individuals (9–11). On the other hand, management of T1D in severely obese individuals can be a challenge, with possible deleterious anabolic effects of intensive insulin therapy on body weight, which further exacerbates insulin resistance (11,12). Importantly, several studies have shown that obesity and metabolic syndrome in T1D are associated with the development and progression of micro- and macrovascular complications (8,13,14).

Adjunct pharmacotherapy to target obesity and insulin resistance in obese individuals with T1D has recently gained attention (14). Some studies have shown that adding metformin (15,16), glucagon-like peptide-1 (GLP-1) agonists (17), and sodium–glucose cotransporter 2 inhibitors (18) to insulin therapy can decrease body weight and improve insulin resistance, glycemic control, and comorbid conditions in some obese patients with T1D.

In addition to achieving substantial and long-lasting weight loss, bariatric surgical procedures are known to have favorable effects on components of the metabolic syndrome, including hyperglycemia, dyslipidemia, hypertension, and inflammation (19–21). Multiple randomized clinical trials (22–25) and long-term studies (26,27) have shown significant and durable effects of bariatric surgery on type 2 diabetes (T2D), with possible long-term, complete remission of this progressive disease. Moreover, gastric bypass in patients with T2D can lead to a significant reduction in the predicted risk of major complications including cardiovascular diseases, nephropathy, retinopathy, and mortality at long-term follow-up (28), while enhancing patients' quality of life (22).

In contrast to studies of T2D, there is a paucity of data on the impact of bariatric surgery in T1D. The aim of this review is to summarize and to quantify the overall effects of bariatric surgery in obese patients with T1D.

METHODS

We searched PubMed, Scopus, ISI Web of Knowledge, and Google Scholar from their inception to December 2015 to identify all relevant studies of bariatric surgery in adult patients with T1D, regardless of language or publication status. The following key words were used, both alone and in combination: type 1 diabetes, insulin-dependent diabetes, bariatric, metabolic surgery, diabetes surgery, gastric bypass, gastric banding, sleeve, obesity, morbid obesity, weight loss, and intestinal bypass. Data on study characteristics, baseline characteristics of individuals, and surgical outcomes were abstracted. Studies were categorized as case series (report of five or more patients) and case reports.

Since the glycated hemoglobin (HbA_{1c}) findings were inconsistent among the studies, pooled data were analyzed to clarify the significance of postoperative changes. Pooled mean and SD for pre- and postoperative HbA_{1c} were calculated. Covariance of pre- and postoperative HbA_{1c} was estimated from individual data (covariance = 0.82). Pre- versus postoperative pooled means were compared using a paired t test with a covariance of 0.82 and with a covariance of 0 (as a conservative analysis).

Characteristics of Included Studies

This review included 17 studies with 107 individuals, including 10 case series (29–38) and 7 case reports (39–45) (Table 1). Details of the case series are presented in Table 2. The first case report and series were published in 2004 (46) and 2008 (34), respectively. All other case series (n = 9) (29–33,35–38) were published between 2013 and 2015. Three studies compared the surgical outcomes between T1D and insulin-requiring T2D (31,32,35). All studies had at least 1 year of average postoperative follow-up time. The absence of high-quality studies, the retrospective designs, the small sample sizes, and the short follow-up times are important limitations for all observational case studies reported.

Baseline Characteristics of Patients

Male-to-female ratio was 1:4. All but one study included only severely obese patients; the exception included less obese patients with an average BMI of 29 kg/m^2 (38). In most studies the duration of T1D before bariatric surgery was more than 20 years.

Correct diagnosis of T1D in the presence of severe obesity, combining insulin secretory defects and insulin resistance, can be difficult (11,32,43). According to the International Diabetes Federation statement on the role of bariatric surgery in the management of diabetes, fasting insulin, C-peptide, and pancreatic autoantibody status (islet cell and glutamic acid decarboxylase) should be checked before bariatric surgery (47). One of the causes of persisting diabetes after bariatric surgery may be that the patient actually had undiagnosed autoimmune diabetes, not T2D (48). For example, among a group of patients with T1D who had undergone bariatric surgery, one-third of cases were initially diagnosed as having T2D. It was only after significant weight loss and lack of significant improvement in diabetes that additional testing with autoantibodies and C-peptide yielded an appropriate diagnosis (32).

Surgical Procedures

All four widely accepted bariatric procedures, including Roux-en-Y gastric bypass, adjustable gastric banding, sleeve gastrectomy, and biliopancreatic diversion with duodenal switch, have been reported in patients with T1D. Overall, the dominant procedure was Roux-en-Y gastric bypass (n = 70, 65%). Other reported procedures included loop gastric bypass (mini-gastric bypass) (38) and single-anastomosis duodenoileal bypass (41).

The choice of bariatric surgery in patients with T1D is largely surgeon specific because of the lack of trials directly comparing surgical procedures in this patient population. For patients with T2D, the diversionary bariatric procedures demonstrate more pronounced metabolic benefits related to greater weight loss and weight-independent effect than nondiversionary procedures. In appropriate-risk patients with T1D, gastric bypass offers a treatment option with a risk/benefit profile that lies between purely restrictive (gastric banding) and malabsorptive (duodenal switch) procedures (12,19,22,27,49). Sleeve gastrectomy is a newer surgical procedure and provides metabolic effects, weight loss, and surgical risks that are intermediate between gastric banding and gastric bypass. Sleeve gastrectomy is believed to lead to a more predictable absorption of carbohydrates

Table 1—Observational studies of bariatric surgery in patients with T1D and changes in HbA_{1c}

Author	Year	Patients (*n*)	Preoperative HbA_{1c}, % (mmol/mol)	Postoperative HbA_{1c}, % (mmol/mol)	*P* value
Lannoo et al. (29)	2014	22	8.4 ± 1.1 (68 ± 12)*	8.2 ± 1.0 (66 ± 10.5)	0.47
Brethauer et al. (30)	2014	10	10.0 ± 1.6 (86 ± 17.5)	8.9 ± 1.1 (74 ± 12)	0.039
Robert et al. (31)	2015	10	7.5 ± 0.8 (58 ± 8.7)	7.1 ± 0.9 (54 ± 9.8)	0.52
Maraka et al. (32)‡	2015	10	8.4 ± 1.5 (68 ± 16.4)	7.9 ± 0.8 (63 ± 8.7)	0.172*
Middelbeek et al. (33)	2015	10	8.1 ± 1.3 (65 ± 14.2)	8.3 ± 1.4 (67 ± 15.3)	0.47
Smith et al. (34)**	2008	9	11.9 ± NR (107 ± NR)	NR	NR
Blanco et al. (35)	2014	7	8.3 ± 1.2 (67 ± 13.1)	8.2 ± 0.9 (66 ± 9.8)	1
Tang et al. (36)	2014	6	8.1 ± 1.3 (65 ± 14.2)	8.2 ± 1.6 (66 ± 17.5)	>0.05
Raab et al. (37)	2013	6	8.2 ± 1.1 (66 ± 12)*	7.2 ± 0.7 (55 ± 7.7)*	0.144*
Garciacaballero et al. (38)	2013	5	8.3 ± 1.5 (67 ± 16.4)	6.7 ± 0.4 (50 ± 4.4)	0.041*
Czupryniak et al. (39)	2010	1 1 1	9.5 (80) 11.1 (98) 10.5 (91)	6.9 (52) 7.5 (58) 6.8 (51)	NR
Mendez et al. (40)	2010	1 1 1	8.2 (66) 7.6 (60) 8.1 (65)	7.5 (58) 7.8 (62) 8.8 (73)	NR
Fuertes-Zamorano et al. (41)	2013	1 1	7.6 (60) 7.5 (58)	6.2 (44) 6.9 (52)	NR
Dirksen et al. (42)	2013	1	8.6 (70)	8.8 (73)	NR
Chuang et al. (43)	2013	1	8.8 (73)	8.6 (70)	NR
Reyes Garcia et al. (44)	2013	1	9 (75)	7.2 (55)	NR
Ziemiański et al. (45)**	2014	1	8.8 (73)	NR	NR
Pooled data		96#	8.4 ± 1.3 (68 ± 14.2)	7.9 ± 1.1 (63 ± 12)	0.01^ <0.001^^

Data are mean ± SD unless otherwise indicated. NR, not reported. *Calculated based on the value provided in the report. ‡HbA_{1c} data were not available for one patient. **This study was not included in analysis because of the absence of HbA_{1c} data. #Pooled data for the whole cohort with available HbA_{1c} data (96 out of 107 patients). *P* values of pooled data are based on covariance of pre- and postoperative Hb_{A1c}: ^*P* = 0 and ^^*P* = 0.82.

and fat-soluble nutrients and might thus be a good option for postoperative glycemic management and reducing the risk of hypoglycemia in patients with T1D (29).

Weight and Glycemic Control Outcome

All studies reported a significant reduction in excess weight, which was dependent on the type of surgical procedure. The mean preoperative and postoperative BMI following Roux-en-Y gastric bypass was 41.9 ± 3.0 and 31.0 ± 2.6 kg/m^2, respectively ($P < 0.001$). In three available comparative studies, patients with T1D and insulin-requiring T2D lost similar amounts of weight following bariatric surgery (31,32,35).

A significant reduction in weight-adjusted daily insulin requirements at the last follow-up point was shown in all case series except one (nine studies). That study reported a transient reduction until 8 months following surgery (35).

In contrast to results for weight and insulin requirements, the HbA_{1c} changes were not consistent among the studies, which could be partly explained by the fact that these small reports were not adequately powered to reveal postoperative changes in HbA_{1c}. In addition, differences in study design, patient characteristics, and surgical procedures between studies may account for the reported differences in HbA_{1c} changes (36,50).

In a meta-analysis, pooled mean ± SD of pre- versus postoperative HbA_{1c} for the entire cohort with available data (n = 96) was 8.4 ± 1.3% (68 ± 14.2 mmol/mol) vs. 7.9 ± 1.1% (63 ± 12 mmol/mol), respectively ($P < 0.001$ for analysis using estimated covariance; P = 0.01 for conservative analysis using a covariance of 0) (Table 1).

Impacts on Obesity and Diabetes Comorbidities

Bariatric surgery results in the remission or improvement of many, if not all, of the comorbidities associated with obesity, including hypertension, dyslipidemia, sleep apnea, gastroesophageal reflux disease, liver steatosis, stress urinary incontinence, and musculoskeletal problems (19–28,51,52). Such beneficial effects on obesity-related comorbidities can also be extrapolated to severely obese patients with T1D. Improvement in lipid profile (30–33,38,39,41–44) and blood pressure (30,31,38,39,41,45) was shown in some studies. In one comparative series, remission rates of hypertension and dyslipidemia were similar among patients with T1D and T2D after bariatric surgery (31). A few studies also reported evidence of improvement in sleep apnea (31,43), kidney function and microalbuminuria (30,33,38,39,45), retinopathy (33), and quality of life (38,41,43) after surgery. A reduction in the number and dosage of medications needed to treat diabetes, hypertension, dyslipidemia, and other obesity-related comorbidities following bariatric surgery would be an additional benefit (22–24,27,32).

Adverse Events After Surgery

Overall, bariatric surgery is safe in patients with T2D, with short-term morbidity and mortality comparable to those of common procedures such as cholecystectomy and appendectomy (49). Improvement in surgical techniques, formal fellowship training, and

Table 2—Case series of bariatric surgery in patients with T1D

Author	Patients (*n*)	Procedures (*n*)	Follow-up (years)#	Female sex (*n*)	Age (years)#	Duration of T1D (years)#	Baseline BMI (kg/m^2)#	Significant reductions: In excess weight	Significant reductions: In HbA_{1c}§	Significant reductions: In insulin requirement	Other reported benefits
Lannoo et al. (29)	22	RYGB (16), SG (6)	3	NR	NR	NR	40	Yes (40 vs. 31 kg/m^2)	No	Yes (0.8 vs. 0.5 IU/kg/day)	—
Brethauer et al. (30)	10	RYGB (7), AGB (2), SG (1)	3	9	46	22	42	Yes (42 vs. 30 kg/m^2)	Yes	Yes (0.7 vs. 0.4 IU/kg/day)	Improvement in lipid profile, hypertension, and albuminuria
Robert et al. (31)	10	BPD-DS (7), SG (3)	4.5	8	39	23	47	Yes 70% (46 kg loss)	No	Yes (1.1 vs. 0.4 IU/kg/day)	Improvement in lipid profile, hypertension, and sleep apnea
Maraka et al. (32)	10‡	RYGB (9), SG (1)	2	7	51	22	44	Yes (44 vs. 31 kg/m^2)	No	Yes (93 vs. 41 IU/day)*	Less use of lipid-lowering medications
Middelbeek et al. (33)	10	RYGB (10)	5	10	40	25	44	Yes (44 vs. 34 kg/m^2)	No	Yes (0.42 vs. 0.37 IU/kg/day)	Improvement in HDL, albuminuria, and retinopathy
Smith et al. (34)	9	RYGB (9)	1	4	46	16	NR	NR	NR	Yes	—
Blanco et al. (35)	7	RYGB (7)	2	7	38	NR	39	Yes (39 vs. 27 kg/m^2)	No^	No^^ (0.6 vs. 0.6 IU/kg/day)	—
Tang et al. (36)	6	RYGB (1), SG (2), AGB (3)	1.3	6	36	18	46	Yes (46 vs. 35 kg/m^2)	No	Yes (75 vs. 39 IU/day)*	—
Raab et al. (37)	6	BPD-DS (3), RYGB (2), SG (1)	1*	6	43*	17	42*	Yes (42 vs. 28 kg/m^2)*	No	Yes (0.9 vs. 0.5 IU/kg/day)*	—
Garciacaballero et al. (38)	5	Mini-gastric bypass (5)	1*	2	37*	25*	29*	Yes (29 vs. 22 kg/m^2)*	Yes	Yes (61 vs. 13 IU/day)*	Improvement in quality of life, lipid profile, hypertension, and nephropathy

AGB, adjustable gastric banding; BPD-DS, biliopancreatic diversion with duodenal switch; NR, not reported; RYGB, Roux-en-Y gastric bypass; SG, Sleeve gastrectomy. #Data are mean or median, based on availability. ‡HbA_{1c} data were not available for one patient. ^A transient improvement until 4 months was observed. ^^A transient improvement until 8 months following surgery was observed. *Calculated based on the value provided in the report. §HbA_{1c} data are detailed and analyzed in Table 1.

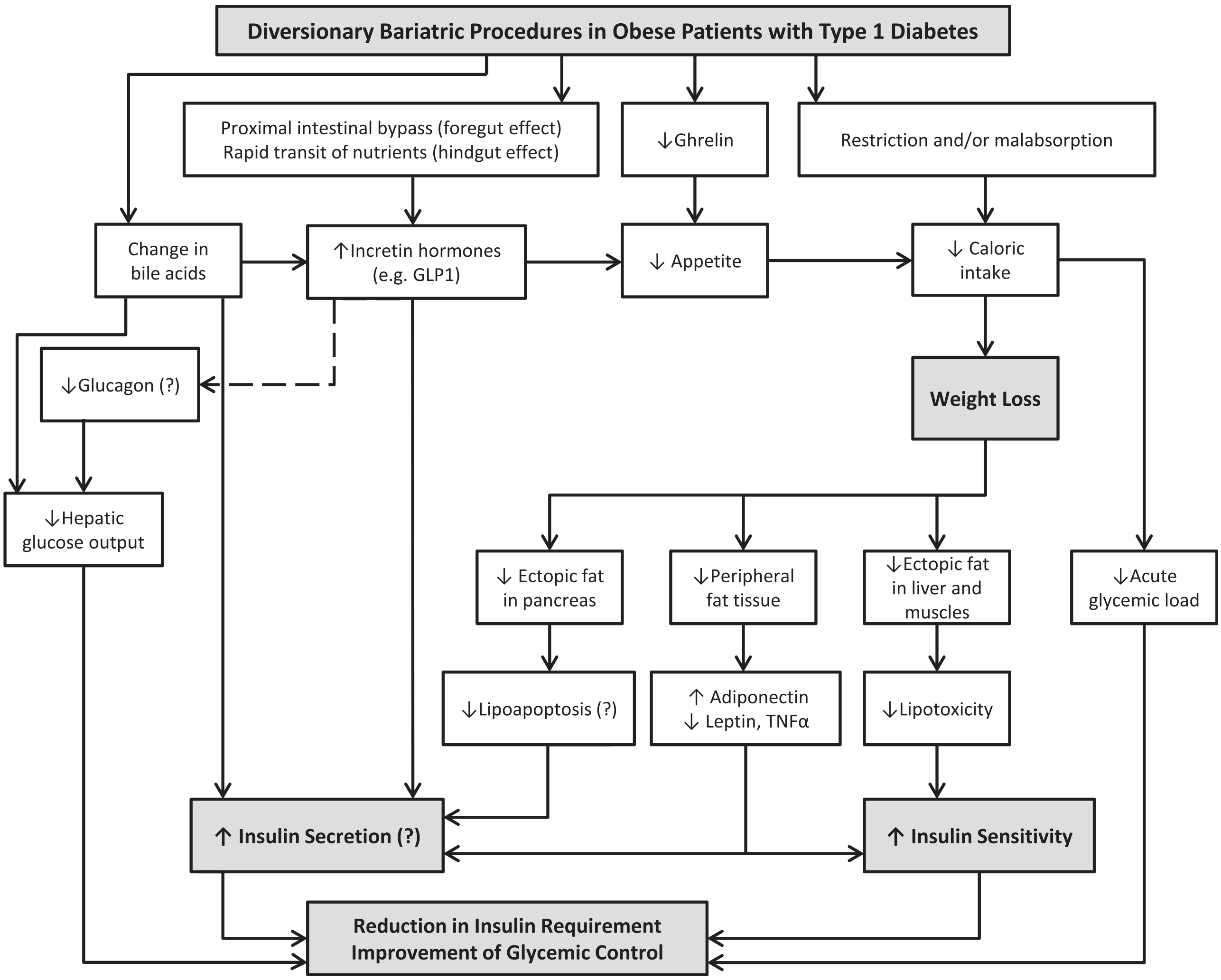

Figure 1—Proposed mechanism of action of gastrointestinal bypass procedures in obese patients with T1D. TNFα, tumor necrosis factor α.

perioperative management protocols, along with implementation of national accreditation programs for bariatric surgery centers, has led to continuous improvement in the surgical safety profile (49,53–55).

This review may underestimate the rate of postoperative adverse events primarily as a result of underreporting by small, retrospective, observational case studies. No mortality was reported among the 107 cases with T1D. In addition to known but uncommon postoperative complications of bariatric surgery, such as bleeding, gastrointestinal leak, marginal ulcer (29,30), and venous thromboembolism (30), two types of adverse events in patients with T1D are noteworthy.

Profound glycemic changes (diabetic ketoacidosis [DKA] and severe hypoglycemia) following surgery have been reported in this population (30,32,38,39,43). Altering the gastrointestinal anatomy can change glucose absorption kinetics. The new glucose kinetics can complicate matching insulin titration with glucose excursions, which can lead to profound hypo- and hyperglycemia. In addition, uncontrolled preoperative hyperglycemia, anesthesia and surgical stress, poor perioperative insulin adjustment, postoperative infection, and poor oral intake/dehydration after surgery can predispose patients to DKA (43,56). The incidence of postoperative DKA is 20–25% in some reports (32,57). Perioperative and long-term postsurgical management of diabetes by an endocrinologist or a diabetes educator is indicated to minimize the risk of metabolic complications related to hypoglycemic episodes and DKA.

Gastrointestinal dysmotility symptoms such as prolonged ileus, intractable nausea and vomiting (30), and acute gastric remnant dilation (58) have also been reported in patients with T1D after bariatric surgery. Autonomic neuropathy and gastroparesis can complicate the postoperative course of patients with prolonged T1D.

Mechanism of Action

The precise mechanisms for improved glycemic status after bariatric surgery in patients with T1D are not clear. Autoimmune β-cell destruction is a hallmark of T1D that affects impaired insulin secretion. The rate of destruction, however, can vary (59,60). In patients with T2D, bariatric surgery improves pancreatic islet size, function, and survival (61,62). However, there is no evidence that patients with prolonged T1D with minimal or no residual β-cell activity can regenerate and reproduce an adequate level of insulin secretion following bariatric surgery. Therefore, the observed reduction of HbA_{1c} in T1D cannot be as good as reported outcomes of bariatric surgery in patients with T2D (31,32,35). However, surgically induced weight loss reduces lipotoxicity in the liver and skeletal muscles, and attenuates the proinflammatory environment associated with obesity, which can lead to reduced obesity-related insulin resistance (63–66). Reductions in caloric intake and altered proportions of macronutrients can also contribute to lower insulin requirements (56). The role of incretin hormones such as GLP-1 on improved glycemic control in T2D following diversionary bariatric procedures has attracted much interest in recent years (63–67). The incretin mechanism may also contribute to improved glucose metabolism in patients with T1D after bariatric surgery (35,42) by inhibiting glucagon secretion even in the absence of residual β-cells. A clinical study showed that 4 weeks of treatment with liraglutide (GLP-1 receptor analog) reduced insulin dose, with improved or unaltered glycemic control in patients with T1D with and without residual β-cell function. The treatment effect was larger in patients with residual β-cell function (with detectable C-peptide), and some patients were able to discontinue insulin treatment (68). An experimental study of a rat model of spontaneous development of T1D showed that a diversionary gastrointestinal procedure (duodenal-jejunal bypass surgery) lowers blood glucose concentrations within 2 days after surgery, which occurred independent of weight loss and insulin secretion (69). In one case series of T1D, the reduction in basal insulin requirements shortly after gastric bypass did not correlate with the extent of weight loss, suggestive of weight loss–independent mechanisms (56). The proposed mechanisms of bariatric surgery in obese patients with T1D are shown in Fig. 1.

SUMMARY

It is expected that the need for bariatric surgery in patients with T1D will increase in the future, since the prevalence of severe obesity among this population has considerably increased during the past decade (70). Impaired glycemic control, which commonly occurs in patients with T1D and severe obesity (11,14), can have deleterious effects on cardiovascular status, kidney function, vision, and survival (3,8,13).

The findings of this review and analysis indicate that bariatric surgery leads to substantial weight loss in severely obese patients with T1D and results in a significant improvement in insulin requirements and glycemic status. The favorable metabolic effects of bariatric surgery may facilitate medical management of T1D in the setting of severe obesity. Nonetheless, optimal glycemic control is still difficult to achieve in some patients after bariatric surgery. The most recent (2015) guidelines of the American Diabetes Association indicate that "although bariatric surgery has been shown to improve the metabolic profiles of morbidly obese patients with T1D, the role of bariatric surgery in such patients will require larger and longer studies" (71).

It is unclear whether decreased caloric intake, weight loss, hepatic glucose production, or improved intestinal biology (e.g., incretins, bile acids) and insulin action account for the postsurgical improvement in insulin requirements and glycemic status in T1D, as observed in patients with obesity and T2D (50).

In addition to the positive impact on glycemic control, bariatric surgery may also be beneficial for cardiovascular health by reducing hypertension and dyslipidemia in obese patients with T1D. Improvements in kidney function and quality of life have also been reported after bariatric surgery in this population. Results of this review also indicate that bariatric surgery is a relatively safe surgical procedure in patients with T1D. However, results are limited to short follow-up and are based on a small number of observational studies and individuals.

In conclusion, short-term results of bariatric surgery in patients with T1D are promising, but additional experimental and prospective clinical studies are necessary. Further investigations are needed to understand better the contribution of altered intestinal biology, dietary macro- and micronutrient changes, activity patterns, adherence to scheduled insulin, and the impact of other obesity-related comorbidities following various bariatric surgical procedures on glucose metabolism in patients with T1D.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.
Author Contributions. A.A. developed the concept, designed the study, collected data, performed analysis, and wrote the manuscript. J.P.K., S.R.K., B.B., S.A.B., and P.R.S. reviewed and edited the final version of the manuscript.

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